Competitive Solvent Extraction of Alkali Metal Cations into Chloroform by Lipophilic Acyclic Proton-Ionizable Polyethers

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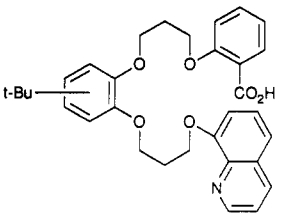
A series of lipophilic acyclic polyether carboxylic acids and a corresponding polyether phosphonic acid monoethyl ester were synthesized in which the unit that contains the lipophilic and the proton-ionizable groups is held constant, but the polyether chain and its terminal group are systematically varied. Competitive solvent extraction of alkali metal cations from aqueous solutions into chloroform was performed to assess the influence of structural variation within the extractant molecule upon the extraction selectivity and efficiency. Many of the ionophores exhibited extraction selectivity for Li^+. One of the simplest chelating agents gave an extraction selectivity order of $Li^+ \gg Na^+ > K^+, Rb^+ > Cs^+$ and a Li^+/Na^+ selectivity ratio of 4.9, while the selectivity ratios for Li^+ over K^+, Rb^+, and Cs^+ were 12 or higher.

INTRODUCTION

The naturally occurring polyether ionophores nigericin, monensin A, and Lasalocid A mediate active ion transport through lipophilic biological membranes by formation of hydrophobic complexes with metal cations.[1] The ionophores adopt a conformation by head-to-tail hydrogen bonding between terminal carboxylate and alcohol groups forming pseudocavities which selectively bind the metal ions.[2]

Synthetic mimics of the carboxylate antibiotics, e.g. 1–4, have been prepared by Hiratani and co-workers[3-6] and by Nakahama and co-workers.[7-12] NMR evidence was obtained by both groups which suggests that the complexes involve coiled structures of the ligands around the cations.[6,9] In the crystal structure of the potassium carboxylate salt of 4, the pseudocyclic polyether backbone wraps around K^+ like the seams of a tennis ball.[12]



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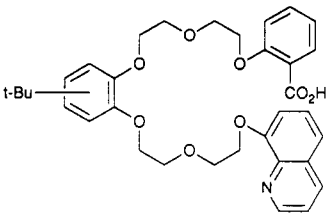

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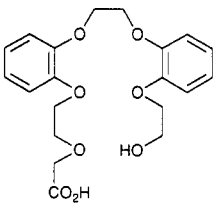

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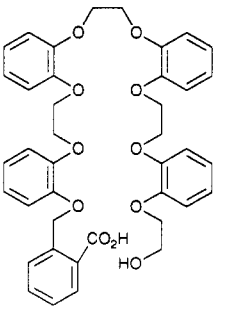

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We have reported the synthesis[13,14] and alkali metal cation extraction behavior[15,16] of the lipophilic crown ether carboxylic acids 5. For crown ether carboxylic acids 5 with ring sizes of 12-crown-4, 15-crown-5, 18-crown-6, and 21-crown-7, solvent extraction selectivities for Li^+, Na^+, K^+, and Cs^+, respectively, were observed as would be predicted from the polyether cavity diameters. Compared with neutral crown ethers, ligands such as 5 have the important advantage that extraction of a metal ion from the aqueous phase into the organic medium does not require concomitant transport of an aqueous phase anion.

To search for a possible pseudocyclic effect in analogous acyclic polyether carboxylic acids for which hydrogen bonding of a terminal alcohol function with a carboxylate group would from a pseudoring structure (e.g., 6), the lipophilic acyclic polyether alcohols 7–10 have now been prepared and their solvent extraction behavior toward alkali metal cations evaluated. For comparison, solvent extraction experiments were also conducted with 11 and 13–15, which are the synthetic precursors to 7–10, respectively, and with structurally related compounds 12 and 16.

EXPERIMENTAL SECTION

Apparatus. Melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were obtained with either a Nicolet MX-S or a Beckman Aculab 8

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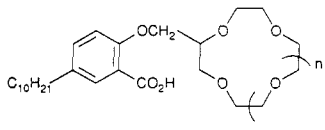
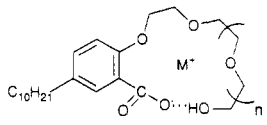
Table I. Yields, Physical Properties, and Spectral Data for Compounds 17–28

compd no.	yield, %	bp, °C/Torr	^{1}H NMR spectra[a] (60 MHz), ppm	IR spectra,[b] cm^{-1}
17	59	81–84/0.06[c]	3.00–4.10 (m, 5 H), 4.45 (s, 2 H), 7.28 (s, 5 H)	3412 (OH), 1125 (CO)
18	50	114–116/0.15	3.08–4.00 (m, 9 H), 4.56 (s, 2 H), 7.32 (s, 5 H)	3431 (OH), 1101 (CO)
19	38	164–167/0.7	3.10–4.08 (m, 13 H), 4.53 (s, 2 H), 7.30 (s, 5 H)	3548 (OH), 1099 (CO)
20	63	210–212/0.15	2.95–4.15 (m, 17 H), 4.52 (s, 2 H), 7.30 (s, 5 H)	3458 (OH), 1196 (CO)
21	84	*d*	2.36 (s, 3 H), 3.35–4.67 (m, 6 H), 6.50–8.00 (m, 9 H)	1354, 1186 (SO_2), 1097 (CO)
22	83	*d*	2.30 (s, 3 H), 2.90–4.68 (m, 10 H), 6.55–7.90 (m, 9 H)	1354, 1180 (SO_2), 1097 (CO)
23	87	*d*	2.29 (s, 3 H), 3.00–4.68 (m, 14 H), 6.68–7.90 (m, 9 H)	1359, 1176 (SO_2), 1091 (CO)
24	74	*d*	2.40 (s, 3 H), 3.08–4.62 (m, 13 H), 6.80–7.88 (m, 9 H)	1359, 1188 (SO_2), 1097 (CO)
25	45	*d*	0.40–2.00 (m, 19 H), 2.50 (t, 2 H), 3.40–4.88 (m, 9 H), 6.68–7.90 (m, 8 H)	1732 (C=O), 1082 (CO)
26	50	*d*	0.45–2.00 (m, 19 H), 2.54 (t, 2 H), 3.22–4.64 (m, 13 H), 6.52–7.70 (m, 8 H)	1730 (C=O), 1082 (CO)
27	44	*d*	0.45–2.00 (m, 19 H), 2.50 (t, 2 H), 3.32–4.75 (m, 17 H), 6.68–7.72 (m, 8 H)	1732 (C=O), 1105 (CO)
28	40	*d*	0.55–2.00 (m, 19 H), 2.50 (t, 2 H), 3.50–4.70 (m, 12 H), 6.80–7.95 (m, 8 H)	1732 (C=O), 1107 (CO)

[a] Measured in $CDCl_3$. [b] Neat. [c] Literature[18] bp = 95 °C/0.25 Torr. [d] Colorless oil.



5 (n = 1-7)



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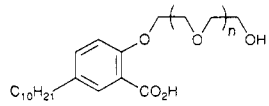

n	
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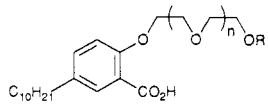
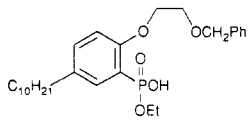
8	1
9	2
10	3



n	R	
11	0	CH_2Ph
12	0	CH_3
13	1	CH_2Ph
14	2	CH_2Ph
15	3	CH_2Ph



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spectrophotometer and are reported in reciprocal centimeters. ^{1}H NMR spectra were recorded with a Varian EM-360 spectrometer and chemical shifts are reported in parts per million (δ) downfield from TMS. Elemental analysis were performed by Integral Microanalytical Laboratories of Raleigh, NC, and by Galbraith Laboratories of Knoxville, TN. Alkali metal cation concentrations in the aqueous phases were determined with a Dionex Model 10 ion chromatograph. Concentrations of the ionophores in the chloroform solutions were measured with a Cary Model 17 UV–vis spectrophotometer. pH measurements were performed with a Fisher Accumet Model 620 pH meter using a Corning No. 476050 combination electrode.

Reagents. Sources of reagent-grade inorganic chemicals and the methods of solvent purification were the same as reported.[17] Organic reagents were reagent-grade and were used as received from commercial suppliers. THF was purified by distillation from lithium aluminum hydride. Pyridine and pentane were dried over NaOH.

Preparation of Monobenzyl-Protected Ethylene Glycol and Oligoethylene Glycols (17–20). Benzyl chloride (30.0 g, 0.23 mol) was added to 1.31 mol of the glycol, 9.8 g of NaOH, and 9.8 mL of water. The mixture was heated at 100 °C for 24 h, cooled to room temperature, poured into 250 mL of water, and extracted with diethyl ether. The ether layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was distilled under high vacuum to afford the monobenzyl-protected glycol. Yields, boiling points, and spectral data for **17–20** are given in Table I.

Preparation of Tosylates 21–24. To a solution of *p*-toluenesulfonyl chloride (0.05 mol) in 10 mL of pyridine at −5 °C was added dropwise a solution of the benzyl-protected glycol **17–20** (0.05 mol) in 15–20 mL of pyridine. The solution was placed in a refrigerator for 16–18 h, and then a cold solution of concentrated HCl (40 mL) and water (100 mL) was added. The aqueous mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give the corresponding tosylate as a colorless oil. Yields and spectral data of **21–24** are presented in Table I.

Preparation of Esters 25–28. NaH (0.34 g, 50% dispersion in mineral oil, 7.0 mmol) was washed with pentane under nitrogen to remove the mineral oil and was suspended in 20 mL of THF. A solution of methyl 5-decylsalicylate[14] (1.75 g, 6.0 mmol) in 20 mL of THF was added dropwise with stirring at room temperature under nitrogen. After 2 h, a solution of 6.0 mmol of the tosylate **21–24** in 20 mL of THF was added dropwise, and the reaction mixture was stirred and refluxed for 48 h. The solvent was evaporated in vacuo, and the residue was dissolved in chloroform and washed with water. The organic layer was dried over $MgSO_4$ and evaporated in vacuo to yield the crude product which was purified by passage through a short column of silica gel with petroleum ether/EtOAc (3:1) as eluent to give the corresponding ester as a colorless oil. Yields and spectral data for **25–28** are recorded in Table I.

Preparation of Lipophilic Acyclic Polyether Carboxylic Acids 11 and 13–15. To a solution of the ester **25–28** in 10 mL of ethanol was added 10 mL of 10% aqueous NaOH. The mixture was refluxed for 24 h and was filtered. The filtrate was acidified to pH 1 with 6 N HCl and extracted with dichloromethane (3 × 10 mL). The combined extracts were dried over $MgSO_4$ and evaporated in vacuo to give the carboxylic acid as a colorless oil. Yields, spectral data, and elemental analysis data for **11, 13–15** are given in Table II.

Preparation of Lipophilic Acyclic Polyether Carboxylic Acid Alcohols 7–10. To a solution of the carboxylic acid **11, 13–15** (4.4 mmol) in 50 mL of ethanol were added 10% palladium on carbon (100 mg/g of benzyloxy compound) and a catalytic amount of *p*-toluenesulfonic acid. After hydrogenolysis with 2 atm of hydrogen for 24 h, the catalyst was filtered and the filtrate was evaporated in vacuo to provide the acids **7–10**. Yields, physical properties, spectral data, and elemental analysis data for **7–10** are presented in Table II.

Preparation of Lipophilic Acyclic Polyether Carboxylic Acid 12. By the procedure described above for the preparation of tosylates **25–28**, 2-methoxyethanol was converted into its tosylate in 70% yield. To a suspension of KH (0.80 g, 35% dispersion in mineral oil, 7.2 mmol) in 10 mL of THF under nitrogen was added a solution of methyl 5-decylsalicylate (1.90

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Table II. Yields, Physical Properties, Spectral Data, and Elemental Analysis Data for Lipophilic Carboxylic Acids 7–15

compd no.	yield, %	^{1}H NMR spectra[a] (60 MHz), ppm	IR spectra,[b] cm^{-1}	elem analysis	theory	found
7	81[c]	0.45–1.90 (m, 19 H), 2.50 (t, 2 H), 3.30–4.50 (m, 4 H), 6.70–8.40 (m, 4 H)	3279 (OH), 1716 (C=O), 1084 (C–O)	C	70.78	70.65
				H	9.38	9.18
8	78[d]	0.50–2.00 (m, 19 H), 2.50 (t, 2 H), 3.20–4.65 (m, 8 H), 6.50–8.10 (m, 5 H)	3300 (OH), 1734 (C=O), 1132 (C–O)	C	68.82	68.90
				H	9.35	9.22
9	64[c]	0.65–1.90 (m, 19 H), 2.60 (t, 2 H), 3.30–4.60 (m, 12 H), 6.10 (br s, 1 H), 6.70–8.10 (m, 4 H)	3277 (OH), 1732 (C=O), 1124 (C–O)	C	67.29	67.10
				H	9.33	9.36
10	74[d]	0.55–2.10 (m, 19 H), 2.60 (t, 2 H), 3.30–4.80 (m, 16 H), 5.70–8.10 (m, 5 H)	3281 (OH), 1732 (C=O), 1126 (C–O)	C	66.05	65.71
				H	9.31	9.42
11	55[e]	0.45–1.90 (m, 19 H), 2.45 (t, 2 H), 3.40–4.80 (m, 6 H), 6.65–8.00 (m, 8 H)	3277 (COOH), 1732 (C=O), 1105 (C–O)	C	75.69	75.85
				H	8.80	8.90
12	89[f]	0.60–1.90 (m, 19 H), 2.60 (d, 2 H), 3.40 (s, 3 H), 3.60–3.90 (m, 4 H), 4.15–4.45 (m, 2 H), 7.25–7.45 (m, 2 H), 7.90 (d, 1 H)	3277 (COOH),[g] 1732 (C=O), 1130 (C–O)	C	71.39	71.12
				H	9.59	9.32
13	87[e]	0.50–2.00 (m, 19 H), 2.60 (t, 2 H), 3.43–4.80 (m, 10 H), 6.70–8.08 (m, 8 H)	3279 (COOH), 1732 (C=O), 1103 (C–O)	C	73.65	73.53
				H	8.83	8.71
14	90[e]	0.40–2.00 (m, 19 H), 2.60 (t, 2 H), 3.10–4.70 (m, 14 H), 6.50–8.10 (m, 8 H)	3279 (COOH), 1732 (C=O), 1109 (C–O)	C	71.97	72.11
				H	8.86	8.90
15	92[e]	0.45–2.00 (m, 19 H), 2.60 (t, 2 H), 3.20–4.80 (m, 18 H), 6.10–8.15 (m, 8 H)	3279 (COOH), 1732 (C=O), 1107 (C–O)	C	70.56	70.31
				H	8.88	8.99

[a] Measured in $CDCl_3$. [b] Neat. [c] Colorless oil which solidified on standing. [d] Colorless semisolid. [e] Colorless oil. [f] Mp = 56–57 °C. [g] KBr.

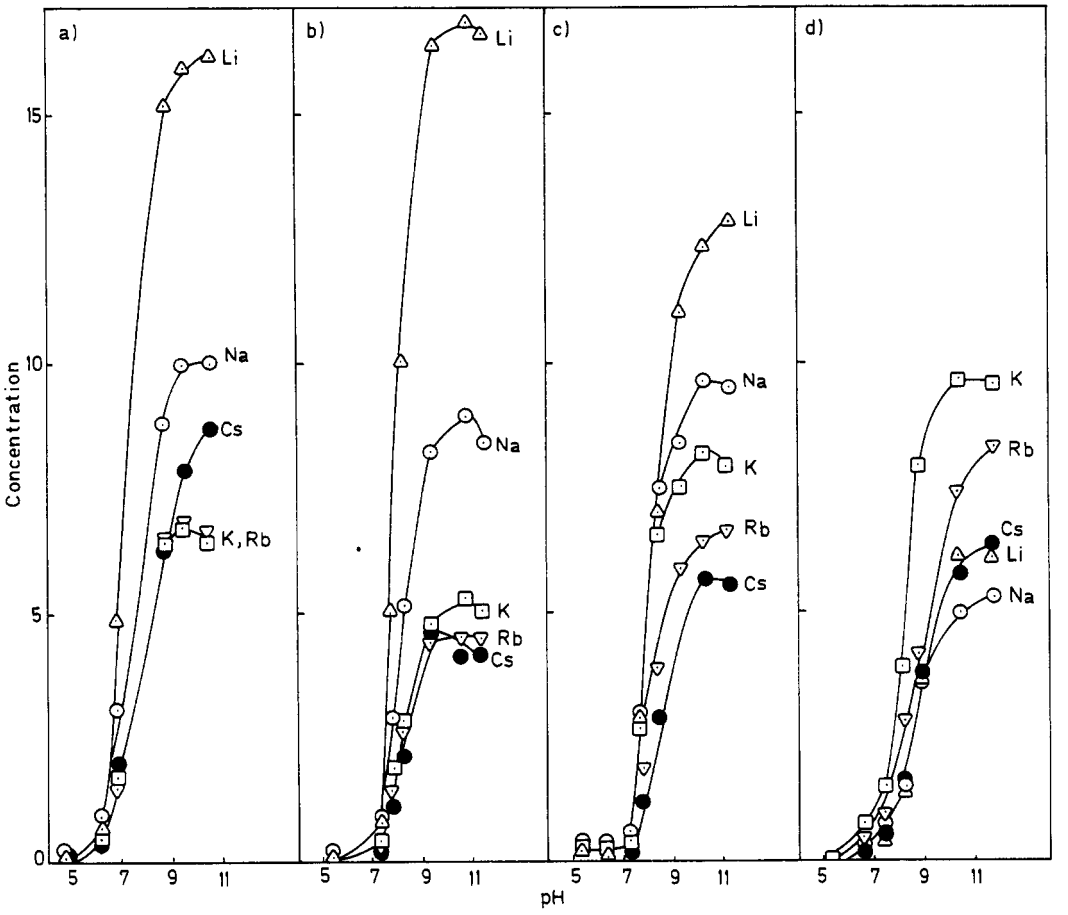


Figure 1. Molar concentrations of metals (×10^3) in the chloroform phase vs the equilibrium pH of the aqueous phase for competitive extraction of 0.25 M alkali metal cations by 0.050 M (a) **7**, (b) **8**, (c) **9**, and (d) **10**.

g, 6.5 mmol) in 10 mL of THF, and the mixture was stirred for 1 h. A solution of the tosylate of 2-methoxyethanol (1.62 g, 7.0 mmol) in 10 mL of THF was added, and the mixture was stirred and refluxed for 3 days. The solvent was evaporated in vacuo, and water was added to the residue. The aqueous mixture was extracted with dichloromethane. The organic extract was dried over $MgSO_4$ and evaporated in vacuo. The residue was passed through a short column of alumina with petroleum ether/EtOAc (3:1) as eluent to give a 69% yield of the coupled product which was refluxed with 10% aqueous NaOH and ethanol (1:1) for 22 h. The ethanol was evaporated in vacuo, and the aqueous residue was acidified to pH 1 with 6 N HCl and extracted with dichloromethane. The extract was dried over $MgSO_4$ and evaporated in vacuo to provide 1.40 g (89%) of **12** as a white solid with mp 56–57 °C. Spectral and elemental analysis data for **12** are given in Table II.

Preparation of Lipophilic Acyclic Polyether Phosphonic Acid Monoethyl Ester 16. To a suspension of KH (0.57 g, 35% dispersion in mineral oil, 5.0 mmol) in 10 mL of THF under nitrogen was added dropwise a solution of 1.51 g (4.1 mmol) of diethyl 5-decyl-2-hydroxybenzenephosphonate[19] in 10 mL of THF. The mixture was stirred for 30 min, and a solution of

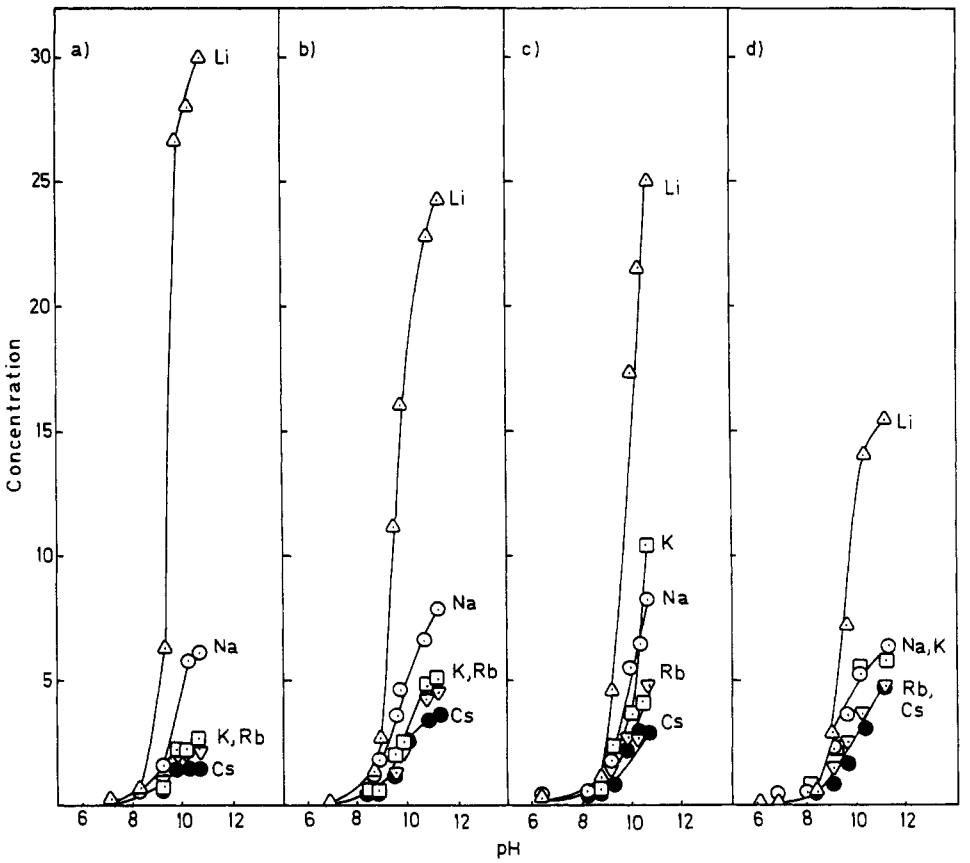
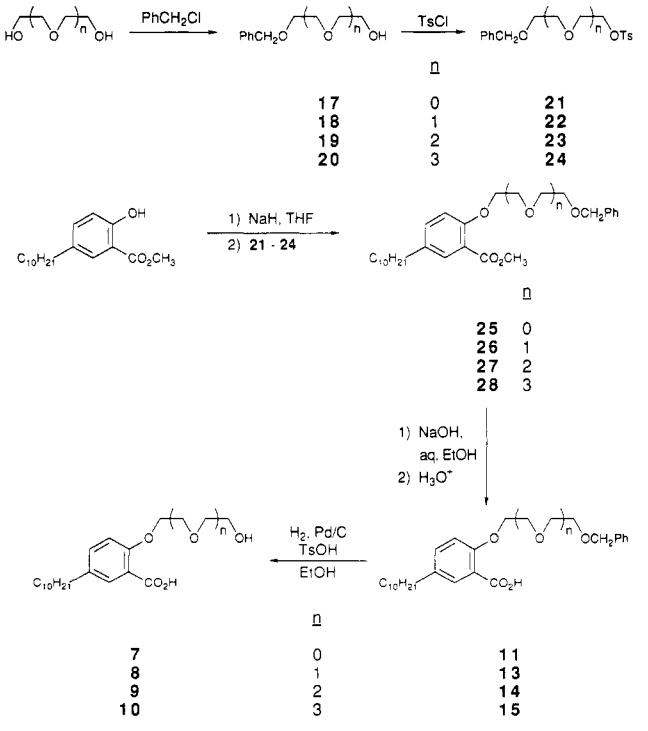


Figure 2. Molar concentrations of metals ($\times 10^3$) in the chloroform phase vs the equilibrium pH of the aqueous phase for competitive extraction of 0.25 M alkali metal cations by 0.050 M (a) **11**, (b) **13**, (c) **14**, and (d) **15**.

Scheme I



n		
17	0	21
18	1	22
19	2	23
20	3	24
25	0	
26	1	
27	2	
28	3	
7	0	11
8	1	13
9	2	14
10	3	15

tosylate **21** (1.40 g, 4.6 mmol) in 10 mL of THF was added dropwise. The mixture was stirred for 1 h at room temperature and then refluxed for 4 days. The solvent was evaporated in vacuo, and the residue was dissolved in water. The aqueous solution was acidified to pH 1 with 6 N HCl and extracted with dichloromethane (3 × 40 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on alumina with petroleum ether/EtOAc (6:1 and then 3:1) as eluents to provide 1.10 g (78%) of the diester as hygroscopic, pale yellow liquid. The diester was refluxed with 10% aqueous NaOH and ethanol (1:1) for 24 h, and the ethanol was evaporated in vacuo. The aqueous solution was acidified to pH 1 with 6 N HCl and extracted with dichloromethane. Evaporation of the solvent in vacuo produced a hygroscopic white solid which was recrystallized from EtOAc to give 1.00 g (96%) of **16** with mp 92–93 °C: ^{1}H NMR ($CDCl_3$) δ 0.60–2.00 (m, 22), 2.60 (t, 2), 3.60–4.45 (m, 8), 7.25–7.95 (m, 8). Anal. Calcd for $C_{27}H_{41}O_5P \cdot 0.2H_2O$: C, 67.53; H, 8.69. Found: C, 67.75, H, 8.70.

Procedure. A chloroform solution (5.0 mL) of the complexing agent (0.050 M) and 5.0 mL of an aqueous solution of five alkali metal chlorides (0.25 M in each) and cesium hydroxide (for pH regulation) were shaken for 15 min in a 30-mL separatory funnel at room temperature (20–23 °C). (Due to the low extractability of Cs^+ from aqueous solutions into chloroform by the lipophilic acyclic proton-ionizable polyethers, 5.0 M cesium hydroxide was utilized to regulate the pH of the aqueous solution.) The aqueous and organic phases were separated, and the equilibrium pH of the aqueous phase was measured. A small sample (0.025 mL) of the organic phase was diluted to 10.0 mL with chloroform in a volumetric flask, and the absorption of the solution was measured at 273–276 nm to determine the concentration of all forms of the complexing agent in the chloroform layer. Of the remaining organic phase, 4.00 mL was removed and shaken with 4.0 mL of 0.2 M HCl to strip the alkali metal cations from the organic phase into an aqueous solution for analysis by ion chromatography.[17] The reproducibility of this procedure for solvent extraction of alkali metal cations from aqueous solutions into chloroform by lipophilic cyclic polyether carboxylic acids has been demonstrated.[20]

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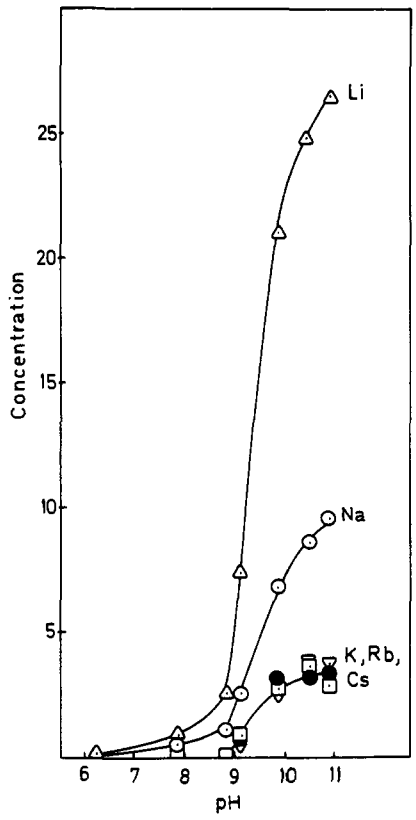

Figure 3. Molar concentrations of metals (×10³) in the chloroform phase vs the equilibrium pH of the aqueous phase for competitive extraction of 0.25 M alkali metal cations by 0.050 M **12**.

RESULTS AND DISCUSSION

Synthesis of New Lipophilic Acyclic Proton-Ionizable Polyethers. The synthetic route to lipophilic acyclic polyether carboxylic acid alcohols **7–10** is shown in Scheme I. Compounds **7–10** provide a series of chelating agents in which the number of ethereal oxygens is systematically varied from one to four. Compounds **11**, **13–15** have the same structures as **7–10** except for replacement of the hydrogen of the alcohol function with a benzyl group. Lipophilic proton-ionizable ethers **12** and **16** were prepared by adaptations of the synthetic route shown in Scheme I. The former is an analog of **11** in which the terminal benzyl group is exchanged for a methyl group. In **16** the carboxylic acid group of **11** is replaced by a phosphonic acid monoethyl ester function.

Solvent Extraction of Alkali Metal Cations from Aqueous Solutions into Chloroform by Lipophilic Acyclic Proton-Ionizable Polyethers. In an earlier investigation of alkali metal cation extraction by a cyclic polyether carboxylic acid,[17] it was found that selectivity orders and efficiencies for competitive extractions in multi-ion systems were quite different from expectations based upon the results of single-ion extractions. Therefore, competitive extractions were utilized in the present study.

A chloroform solution of the extractant (0.050 M) was shaken with an equal volume of an aqueous solution of five alkali metal chlorides and hydroxides (0.25 M in each alkali metal cation). The layers were separated and the equilibrium pH of the aqueous phase was measured. Of the organic phase, a small portion was removed and diluted with chloroform. The absorbance of the solution at 273–276 nm demonstrated no apparent loss of the lipophilic acyclic proton-ionizable polyethers **7–16** from their chloroform solutions even when contacted with highly alkaline aqueous phases. A larger portion of the organic phase was shaken with 0.2 M HCl to strip the extracted alkali metal cations into aqueous solutions for analysis by ion chromatography.

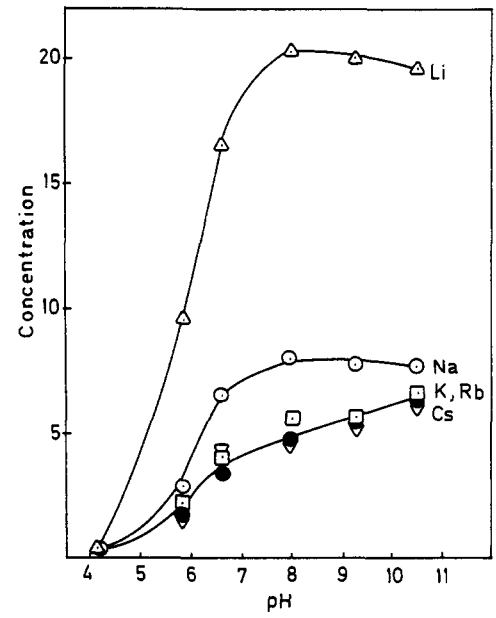

Figure 4. Molar concentrations of metals (×10³) in the chloroform phase vs the equilibrium pH of the aqueous phase for competitive extraction of 0.25 M alkali metal cations by 0.050 M **16**.

Data for competitive extractions of aqueous alkali metal cation solutions by chloroform solutions of lipophilic acyclic polyether carboxylic alcohols **7–10** are presented in Figure 1. As noted for extractions of closely-related lipophilic crown ether carboxylic acids,[16] removal of alkali metal cations from acidic aqueous solutions by **7–10** is ineffective. However from basic aqueous solutions, alkali metal cations are readily extracted.

The selectivity order for extractants **7** and **8** (Figure 1, parts a and b, respectively) which possess one hydroxyl group oxygen and one and two ethereal oxygens, respectively, is $Li^+ > Na^+ > Cs^+ \geq K^+, Rb^+$. With the addition of another ethyleneoxy unit to **8**, the Li^+ selectivity decreases for **9** (Figure 1c) and the selectivity order is $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$. With further elongation of the polyether side arm in **10**, the extractant becomes selective for K^+ (Figure 1d). The variation of extraction selectivity from good Li^+ selectivity with **7** and **8** to diminished Li^+ selectivity with **9** to modest K^+ selectivity with **10** suggests the formation of a head-to-tail pseudocavity (e.g. **6**) for the extraction complex from **10**. Assuming a one-to-one metal ion–polyether alcohol carboxylate extraction complex, the maximal metal loading of the organic phase for **7–10** are 95, 79, 86, and 72%, respectively. Thus all four ionophores are effective extractants for alkali metal cations.

To further probe the importance of pseudocavity formation in extraction complexes with **7–10**, alkali metal cation solvent extractions were investigated for lipophilic acyclic polyether carboxylic acids **11**, **13–15**. In this series of ionophores, the hydrogens of the alcohol functions in **7–10** are replaced by benzyl groups. Data for competitive alkali metal cation extractions from aqueous solutions into chloroform by chelating agents **11**, **13–15** are recorded in Table II.

All four compounds exhibit extraction selectivity for Li^+. For **11**, the extraction selectivity order is $Li^+ \gg Na^+ > K^+, Rb^+ > Cs^+$ with a Li^+/Na^+ selectivity ratio of 4.9 (Figure 2a). For **13** which has an additional ethyleneoxy unit, the extraction selectivity order remains the same but the Li^+/Na^+ selectivity ratio decreases to 3.1 (Figure 2b). With further elongation of the polyether sidearm in **14** and **15**, the extraction selectivity order changes slightly to $Li^+ > Na^+, K^+ > Rb^+, Cs^+$ and the ratio of chloroform-phase concentrations of Li^+ to the second best extracted alkali metal cation becomes 2.4–2.5 (Figure 2, parts c and d). Maximal metal loadings in the

organic phase for **11**, **13–15** are 85, 90, 100, and 63%, respectively. Thus the extraction efficiencies for this series of ionophores remain high and similar in magnitude to those observed for **7–10**.

The change from K^+ extraction selectivity for lipophilic acyclic polyether carboxylic acid **10** to Li^+ extraction selectivity for **15** supports the formation of a head-to-tail pseudocavity in the extraction complex for **10**. Thus the hydrogen bonding interaction in **6** with $n = 2$ which forms a pseudocavity of appropriate size for complexation of K^+ is lost when the alcohol function is changed to a benzyl ether unit.

Due to the high hydration energy of Li^+ relative to the other alkali metal cations,[21] ionophores which exhibit good extraction selectivity for Li^+ are of considerable interest. Since the selectivity of the lipophilic acyclic polyether carboxylic acid **11** for Li^+ extraction surpasses that exhibited by lipophilic crown ether carboxylic acids **5** which have 12-crown-4, 13-crown-4, and 15-crown-4 rings,[15,16] the influence of structural variation for **11** was explored. Ionophores **11** and **12** are the same except for replacement of a benzyl ether terminal group in the former with a methyl ether in the latter. Data for competitive solvent extraction of alkali metal cations from aqueous solution into chloroform by lipophilic acyclic polyether carboxylic acid **12** are shown in Figure 3. The extraction selectivity order is $Li^+ > Na^+ > K^+$, Rb^+, Cs^+, the Li^+/Na^+ selectivity ratio is 2.6, and the metal loading is 90%. Thus the Li^+ extraction selectivity for **12** is significantly lower than that of **11** even though the extraction efficiencies are similar. Examination of Corey–Pauling–Kortum (CPK) space-filling models suggests that when the hydrophobic benzyl group is oriented away from polar carboxylate function, the benzyl ether oxygen in combination with the other ether oxygen and one oxygen of the carboxylate group forms a pocket of appropriate dimensions for Li^+ complexation. The smaller size of a terminal methyl group allows more conformation flexibility and produces a less well-formed pocket.

Ionophores **11** and **16** are identical except for a change of the proton-ionizable group from carboxylic acid to phosphonic acid monoethyl ester. Alkali metal cation solvent extraction data for ionophore **16** are given in Figure 4. Compared with carboxylic acid **11** (Figure 2a), the effective pH range for extractions by phosphonic acid monoethyl ester **16** is broader with appreciable efficiency for extraction from weakly acidic and neutral aqueous solutions as well as basic aqueous media. The extraction selectivity order for **16** is $Li^+ > Na^+ > K^+$, Rb^+, Cs^+ and the metal loading is 92%, but the Li^+/Na^+ selectivity ratio is only 2.5. Thus the extraction efficiencies for phosphonic acid monoethyl ester **16** and carboxylic acid **11** are similar but the Li^+ extraction selectivity of the latter is appreciably greater.

With the exception of **5** which has a 14-crown-4 ring, the Li^+ extraction selectivity for acyclic polyether carboxylic acid **11** surpasses that obtained with a variety of crown ether carboxylic acids.[15,16] In view of the easier synthetic access to **11**, its Li^+ selectivity in competitive extraction of alkali metal cations is noteworthy.

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